Pancytopenia on switching from clozapine to olanzapine: A case report and some unresolved issues

The newer antipsychotics olanzapine and clozapine share a number of structural and functional similarities. However, unlike clozapine, which induces agranulocytosis in about 1% of treated patients, olanzapine is not normally known to cause hematological adverse effects. The hematological effects of olanzapine have been scrutinized in several trials, none of which have found any evidence of hemotoxicity, or effects different from placebo in this regard. These studies have included a trial of 32 olanzapine-treated patients who had previously experienced clozapine-induced agranulocytosis. Olanzapine proved to be safe even in this group. 3

On the other hand, several cases of olanzapine-related agranulocytosis/neutropenia in patients who had received clozapine previously, have also been reported. 2-4 Such hematological side-effects have been proposed to be due to the propensity of olanzapine to prolong neutropenia in patients who developed it with clozapine, or to re-induce it in patients who have recovered from clozapine-induced neutropenia. A residual effect of clozapine or the direct effects of olanzapine are some of the other possibilities. 2 The safe timeframe between the two medications and the risk of neutropenia remains unclear. Such timeframes have usually ranged from a few days to weeks, but periods up to three years have also been reported. 2-4 Some reports have also hinted at a relationship between the dose of olanzapine and the degree of neutropenia 3 but this has never been confirmed. On the whole the number of such reports is still very small and not a single report has been able to demonstrate a causal association with the drug. Nevertheless, such incidences are particularly significant because they suggest the need for caution while switching from clozapine to olanzapine. The following is a description of one such instance.

Case Report

A 40-year-old man with paranoid schizophrenia, symptomatic since 1988 was maintained on clozapine 400 mg/day for six years with white blood cell (WBC) counts between 5000-7000/mm³, absolute neutrophil count (ANC) of 3000-4000/mm³, hemoglobin of 10-11 g% and adequate platelets. Despite good compliance, he had persistent and distressing auditory hallucinations that commanded him to do unwanted things, or would constantly comment on whatever he was doing. The voices would sometimes abuse him and urge him to commit suicide. He remained fearful throughout the day because of these voices. In addition he had other delusions, free-floating anxiety, and distressing mental images. These symptoms responded only partially to clozapine, but he was still unable to function normally.

Thus, it was decided to change him over to olanzapine to achieve better control of his symptoms. After stopping clozapine, a hemogram revealed WBC - 4200/mm³, ANC - 3150/mm³, hemoglobin - 9.7 g%, normal platelets, reticulocyte count of 0.3% and normal liver function tests. Two days later, olanzapine was started at 5 mg/day and then increased to 15 mg/day by the sixth day. Within a week of the commencement of olanzapine, his WBC count had fallen to 2500/mm³, ANC to 1250/mm³, hemoglobin to 7.6 g% and platelets to 90000/mm³. Olanzapine was stopped immediately. The patient was placed in isolation and the possibility of any infection was ruled out. Four days after stopping olanzapine WBC count had further fallen to 1000/mm³ (ANC 600/mm³). Simultaneously, evidence of hypoproteinaemia (total proteins/albumin/globulin= 5.1/2.9/2.2 g%), macrocytes on peripheral blood smear (MCV=105 fL) and deranged liver function tests (total bilirubin/ conjugated=1.4/0.7 mg%; SGOT/SGPT=32/9 IU) were also found. Investigations for malabsorption syndrome (d-xylene test, barium-meal follow through, duodenal biopsy, fecal fat test) were however normal, as were serum ferritin levels. His weight and body mass index (BMI) were also within normal limits.

Four days after stopping olanzapine, his counts had already started improving (WBC=3500/mm³, ANC=2310/mm³). However, B₁₂ deficiency could not be completely ruled out at this juncture. Therefore, empirical treatment for nutritional anaemia (iron, B₁₂, and folate supplements) was started on the fifth day after stopping olanzapine. On the same day WBC counts had increased to 5300/mm³, with ANC of 3180/mm³, hemoglobin – 9.9 g%, adequate platelet counts, reticulocyte count had increased to 4% and liver function tests became normal. RBC counts and morphology were normal at this point. He was subsequently treated with another atypical antipsychotic, risperidone (up to 3 mg/day). Fortunately, he responded well to this drug and within a few weeks his hallucinations, delusions and distressing mental images had remitted while his blood counts remained normal. With the subsequent addition of behavioral treatment even his anxiety symptoms were controlled. He has now been on follow-up for over two years and has continued to improve. When last seen he did not report any problems apart from mild weight gain. Regular blood checks done during this period have shown no abnormality. He was back at work part-time, and seemed to be leading a more or less normal life.
Discussion

Antipsychotics such as clozapine and olanzapine have been associated with neutropenia. Their effects on other blood parameters remain uncertain, though pancytopenia with olanzapine and thrombocytopenia with clozapine has been reported. Thus although the presentation in this patient was one of pancytopenia, neutropenia is the main focus of the discussion.

In all likelihood pancytopenia/neutropenia in this patient was drug-induced as indicated by onset with olanzapine use and rapid improvement on cessation of the drug. A nutritional etiology ($B_{12}$ deficiency) was considered because of associated macrocytes and hypoproteinemia, although the latter could still be drug-induced. However, there was no clinical evidence of malnutrition, all investigations were normal, and the improvement in blood counts was much faster than expected. Despite this it was thought wise to begin empirical treatment for nutritional anemia. However, in retrospect it was quite evident that the improvement in blood counts had started even before initiation of treatment for nutritional anemia. The pattern of fall in counts and their subsequent improvement on stopping olanzapine was also similar to earlier reports. As in previous reports, the exact etiology remained uncertain. It could either have been a residual effect of clozapine, or entirely related to olanzapine. Blood counts were normal throughout the 6 years he was on clozapine and immediately after stopping the drug. This, and the fact that the counts continued to deteriorate for a while even after olanzapine was stopped suggested that olanzapine may have contributed to the hematological abnormality.

However, olanzapine was initiated within the recommended 4-week monitoring period after discontinuation of clozapine. Thus, a residual effect of clozapine cannot be completely ruled out. Prolongation of clozapine-induced neutropenia with olanzapine has been reported previously. The other possibility, therefore, was an additive effect of both drugs. Apart from prolonging clozapine-induced neutropenia, olanzapine has also been reported to induce neutropenia in patients treated with clozapine, and to induce neutropenia in patients who have recovered from clozapine-induced neutropenia. However, this case was different because it underlined the fact that neutropenia in patients who have been switched from clozapine to olanzapine can happen even in patients who do not show any hematological side-effects while on long-term clozapine treatment. Thus, there may be no way at present to predict this severe side-effect. Since the number of such cases is on the rise, a statistical evaluation of the risk of developing hematological sequelae during treatment with olanzapine, and an investigation of the possible risk factors, are areas for future research.

An elucidation of the mechanism of action is also awaited. Clozapine-modified polypeptides have been detected in neutrophils in vivo and in clozapine-treated patients. The binding of clozapine and its reactive metabolites could thus play a part in inducing agranulocytosis/neutropenia. Olanzapine-modified polypeptides have also been detected in neutrophils in vitro, but not in vivo. Moreover, olanzapine metabolites could be reliably detected in vitro using anticlozapine antiserum. This suggests that the structural similarity between clozapine and olanzapine reactive metabolites could have a role in the onset of this side effect.

However, the mechanism of action is still far from clear, and other issues related to the dose of olanzapine and safe intervals for use in clozapine-treated patients also need to be resolved. Till then, cautious initiation and regular blood monitoring will be the prudent measures while switching patients from clozapine to olanzapine.

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References